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(21) International Application Number: PCT/GB99/02738 (22) International Filing Date: 18 August 1999 (18.08.99) (30) Priority Data: 9818124.1 19 August 1998 (19.08.98) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): ELLIS, Jonathan, Henry [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). (74) Agent: STOTT, Michael, J.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: GRIP, HUMAN ADAPTER PROTEIN RELATED TO THE GRB2 FAMILY MEMBER		
(57) Abstract A polypeptide comprising the amino acid sequence shown in Figure 5 or any fragment thereof containing at least the amino acid residues encoded by nucleotide residues 151-459 or any polypeptide having substantially the same sequence and capable of binding to human CD28.		

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SEQUENCE LISTING

<110> Glaxo Group Limited

Ellis, Jon H.

<120> Novel human adapter protein

<130> PU3535

<140>

<141>

<150> GB 9818124.1

<151> 1998-08-19

<160> 46

<170> PatentIn Ver. 2.1

<210> 1

<211> 152

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (5) .. (133)

<220>

<223> Description of Artificial Sequence: Artificial
gene encoding the CD28 cytoplasmic domain

<400> 1

catc gcg cgc agt aag agg agc agg ctc ctg cac agt gac tac atg aac 49

Ala Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn

1

5

10

15

2

atg act cca cgt aga ccg ggt cca acg aga aag cat tac cag ccc tat 97
Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
20 25 30

gca cca cct aga gac ttc gca gcc tat cgc tcc tga gcggccgcag 143
Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
35 40

cgcgcgatg 152

<210> 2

<211> 42

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: Artificial
gene encoding the CD28 cytoplasmic domain

<400> 2

Ala Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
1 5 10 15

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
20 25 30

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
35 40

<210> 3

<211> 152

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificial
gene encoding the CD28 cytoplasmic domain

<400> 3

catcgcgcgcg tgcggccgct caggagcgat aggctgcgaa gtctctaggt ggtgcatagg 60
 gctggtaatg ctttctcggt ggacccggtc tacgtggagt catgttcatt tagtcactgt 120
 gcaggagcct gctcctctta ctgcgcgcga tg 152

<210> 4

<211> 993

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1) .. (993)

<400> 4

atg gaa gct gtt gcc aag ttt gat ttc act gct tca ggt gag gat gaa 48
 Met Glu Ala Val Ala Lys Phe Asp Phe Thr Ala Ser Gly Glu Asp Glu
 1 5 10 15

ctg agc ttt cac act gga gat gtt ttg aag att tta agt aac caa gag 96
 Leu Ser Phe His Thr Gly Asp Val Leu Lys Ile Leu Ser Asn Gln Glu
 20 25 30

gag tgg ttt aag gcg gag ctt ggg agc cag gaa gga tat gtg ccc aag 144
 Glu Trp Phe Lys Ala Glu Leu Gly Ser Gln Glu Gly Tyr Val Pro Lys
 35 40 45

aat ttc ata gac atc cag ttt ccc aaa tgg ttt cac gaa ggc ctc tct 192
 Asn Phe Ile Asp Ile Gln Phe Pro Lys Trp Phe His Glu Gly Leu Ser
 50 55 60

cga cac cag gca gag aac tta ctc atg ggc aag gag gtt ggc ttc ttc 240
 Arg His Gln Ala Glu Asn Leu Leu Met Gly Lys Glu Val Gly Phe Phe
 65 70 75 80

atc atc cgg gcc agc cag agc tcc cca ggg gac ttc tcc atc tct gtc	288
Ile Ile Arg Ala Ser Gln Ser Ser Pro Gly Asp Phe Ser Ile Ser Val	
85 90 95	
agg cat gag gat gac gtt caa cac ttc aag gtc atg cga gac aac aag	336
Arg His Glu Asp Asp Val Gln His Phe Lys Val Met Arg Asp Asn Lys	
100 105 110	
ggc aat tac ttt ctg tgg act gag aag ttt cct tcc cta aat aag ctg	384
Gly Asn Tyr Phe Leu Trp Thr Glu Lys Phe Pro Ser Leu Asn Lys Leu	
115 120 125	
gta gac tac tac agg aca aat tcc atc tcc aga cag aag cag atc ttc	432
Val Asp Tyr Tyr Arg Thr Asn Ser Ile Ser Arg Gln Lys Gln Ile Phe	
130 135 140	
ctt aga gac aga acc cga gaa gac cag ggt cac cgg ggc aac agc ctg	480
Leu Arg Asp Arg Thr Arg Glu Asp Gln Gly His Arg Gly Asn Ser Leu	
145 150 155 160	
gac cgg agg tcc cag gga ggc cca cac ctc agt ggg gct gtg gga gaa	528
Asp Arg Arg Ser Gln Gly Gly Pro His Leu Ser Gly Ala Val Gly Glu	
165 170 175	
gaa atc cga cct tcg atg aac cgg aag ctg tcg gat cac ccc ccg acc	576
Glu Ile Arg Pro Ser Met Asn Arg Lys Leu Ser Asp His Pro Pro Thr	
180 185 190	
ctt ccc ctg cag cag cac cag cac cag cca cag cct ccg caa tat gcc	624
Leu Pro Leu Gln Gln His Gln His Gln Pro Gln Pro Pro Gln Tyr Ala	
195 200 205	
cca gcg ccc cag cag ctg cag cag ccc cca cag cag cga tat ctg cag	672
Pro Ala Pro Gln Gln Leu Gln Gln Pro Pro Gln Gln Arg Tyr Leu Gln	
210 215 220	

5

cac cac cat ttc cac cag gaa cgc cga gga ggc agc ctt gac ata aat 720
 His His His Phe His Gln Glu Arg Arg Gly Gly Ser Leu Asp Ile Asn
 225 230 235 240

gat ggg cat tgt ggc acc ggc ttg ggc agt gaa atg aat gcg gcc ctc 768
 Asp Gly His Cys Gly Thr Gly Leu Gly Ser Glu Met Asn Ala Ala Leu
 245 250 255

atg cat cgg aga cac aca gac cca gtg cag ctc cag gcg gca ggg cga 816
 Met His Arg Arg His Thr Asp Pro Val Gln Leu Gln Ala Ala Gly Arg
 260 265 270

gtg cgg tgg gcc cgg gcg ctg tat gac ttt gag gcc ctg gag gat gac 864
 Val Arg Trp Ala Arg Ala Leu Tyr Asp Phe Glu Ala Leu Glu Asp Asp
 275 280 285

gag ctg ggg ttc cac agc ggg gag gtg gtg gag gtc ctg gat agc tcc 912
 Glu Leu Gly Phe His Ser Gly Glu Val Val Glu Val Leu Asp Ser Ser
 290 295 300

aac cca tcc tgg tgg acc ggc cgc ctg cac aac aag ctg ggc ttc ttc 960
 Asn Pro Ser Trp Trp Thr Gly Arg Leu His Asn Lys Leu Gly Phe Phe
 305 310 315 320

cct gcc aac tac gtg gca ccc atg acc cga taa 993
 Pro Ala Asn Tyr Val Ala Pro Met Thr Arg
 325 330

<210> 5

<211> 330

<212> PRT

<213> Homo sapiens

<400> 5

Met Glu Ala Val Ala Lys Phe Asp Phe Thr Ala Ser Gly Glu Asp Glu
 1 5 10 15

6

Leu Ser Phe His Thr Gly Asp Val Leu Lys Ile Leu Ser Asn Gln Glu
 20 25 30

Glu Trp Phe Lys Ala Glu Leu Gly Ser Gln Glu Gly Tyr Val Pro Lys
 35 40 45

Asn Phe Ile Asp Ile Gln Phe Pro Lys Trp Phe His Glu Gly Leu Ser
 50 55 60

Arg His Gln Ala Glu Asn Leu Leu Met Gly Lys Glu Val Gly Phe Phe
 65 70 75 80

Ile Ile Arg Ala Ser Gln Ser Ser Pro Gly Asp Phe Ser Ile Ser Val
 85 90 95

Arg His Glu Asp Asp Val Gln His Phe Lys Val Met Arg Asp Asn Lys
 100 105 110

Gly Asn Tyr Phe Leu Trp Thr Glu Lys Phe Pro Ser Leu Asn Lys Leu
 115 120 125

Val Asp Tyr Tyr Arg Thr Asn Ser Ile Ser Arg Gln Lys Gln Ile Phe
 130 135 140

Leu Arg Asp Arg Thr Arg Glu Asp Gln Gly His Arg Gly Asn Ser Leu
 145 150 155 160

Asp Arg Arg Ser Gln Gly Gly Pro His Leu Ser Gly Ala Val Gly Glu
 165 170 175

Glu Ile Arg Pro Ser Met Asn Arg Lys Leu Ser Asp His Pro Pro Thr
 180 185 190

Leu Pro Leu Gln Gln His Gln His Gln Pro Gln Pro Pro Gln Tyr Ala
 195 200 205

Pro Ala Pro Gln Gln Leu Gln Gln Pro Pro Gln Gln Arg Tyr Leu Gln
 210 215 220

7

His His His Phe His Gln Glu Arg Arg Gly Gly Ser Leu Asp Ile Asn
 225 230 235 240

Asp Gly His Cys Gly Thr Gly Leu Gly Ser Glu Met Asn Ala Ala Leu
 245 250 255

Met His Arg Arg His Thr Asp Pro Val Gln Leu Gln Ala Ala Gly Arg
 260 265 270

Val Arg Trp Ala Arg Ala Leu Tyr Asp Phe Glu Ala Leu Glu Asp Asp
 275 280 285

Glu Leu Gly Phe His Ser Gly Glu Val Val Glu Val Leu Asp Ser Ser
 290 295 300

Asn Pro Ser Trp Trp Thr Gly Arg Leu His Asn Lys Leu Gly Phe Phe
 305 310 315 320

Pro Ala Asn Tyr Val Ala Pro Met Thr Arg
 325 330

<210> 6

<211> 993

<212> DNA

<213> Homo sapiens

<400> 6

ttatcgggtc atgggtgcc cgtagttggc agggagaag cccagcttgt tgtgcaggcg 60
 gccggtccac caggatgggt tggagctatc caggacctcc accacctccc cgctgtggaa 120
 cccagctcg tcctctcca gggcctcaaa gtcatacagc gcccgggccc accgcactcg 180
 ccctgccgcc tggagctgca ctgggtctgt gtgtctccga tgcattgagg ccgcattcat 240
 ttcactgccc aagccggtgc cacaatgccc atcatttatg tcaaggctgc ctctcgggcg 300
 ttcctggtgg aaatggtggt gctgcagata tcgctgctgt gggggctgct gcagctgctg 360
 gggcgctggg gcatattgcg gaggtgtgg ctggtgctgg tgctgctgca ggggaagggt 420
 cggggggtga tccgacagct tccggttcat cgaaggctcg atttcttctc ccacagcccc 480
 actgaggtgt gggcctccct gggacctcgg gtccaggctg ttgccccggt gacctgggtc 540

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ttctcggggt ctgtctctaa ggaagatctg cttctgtctg gagatggaat ttgtcctgta 600
gtagtctacc agcttattta gggaaggaaa cttctcagtc cacagaaagt aattaccctt 660
gttgtctcgc atgaccttga agtggtgaac gtcacctca tgcctgacag agatggagaa 720
gtccccctggg gagctctggc tggcccgat gatgaagaag ccaacctcct tgcccatgag 780
taagttctct gcctgggtgtc gagagaggcc ttcgtgaaac catttgggaa actggatgtc 840
tatgaaattc ttgggcacat atccttctctg gctcccaagc tccgccttaa accactcctc 900
ttggttactt aaaatcttca aaacatctcc agtgtgaaag ctcagttcat cctcacctga 960
agcagtgaaa tcaaacttgg caacagcttc cat 993

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<210> 7

<211> 240

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (9) .. (239)

<220>

<223> Description of Artificial Sequence: Synthetic
construct

<400> 7

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agcttacc atg ggg ggt tct cat cat cat cat cat cat ggt atg gct agc 50
      Met Gly Gly Ser His His His His His His Gly Met Ala Ser

```

1

5

10

```

atg act ggt gga cag caa atg ggt cgg gat ctg tac gac gat gac gat 98
Met Thr Gly Gly Gln Gln Met Gly Arg Asp Leu Tyr Asp Asp Asp Asp
15          20          25          30

```

```

aag tct aga gga tcc aag ctt atg gaa gct gtt gcc aag ttt gat ttc 146
Lys Ser Arg Gly Ser Lys Leu Met Glu Ala Val Ala Lys Phe Asp Phe

```

35

40

45

9

act gct tca ggt gag gat gaa ctg agc ttt cac act gga gat gtt ttg 194
 Thr Ala Ser Gly Glu Asp Glu Leu Ser Phe His Thr Gly Asp Val Leu
 50 55 60

aag att tta agt aac caa gag gag tgg ttt aag gcg gag ctt ggg a 240
 Lys Ile Leu Ser Asn Gln Glu Glu Trp Phe Lys Ala Glu Leu Gly
 65 70 75

<210> 8

<211> 77

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: Synthetic
 construct

<400> 8

Met Gly Gly Ser His His His His His His Gly Met Ala Ser Met Thr
 1 5 10 15

Gly Gly Gln Gln Met Gly Arg Asp Leu Tyr Asp Asp Asp Asp Lys Ser
 20 25 30

Arg Gly Ser Lys Leu Met Glu Ala Val Ala Lys Phe Asp Phe Thr Ala
 35 40 45

Ser Gly Glu Asp Glu Leu Ser Phe His Thr Gly Asp Val Leu Lys Ile
 50 55 60

Leu Ser Asn Gln Glu Glu Trp Phe Lys Ala Glu Leu Gly
 65 70 75

10

<210> 9

<211> 240

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
construct

<400> 9

tcccaagctc cgccttaaac cactcctctt gggtacttaa aatcttcaaa acatctccag 60
tgtgaaagct cagttcatcc tcacctgaag cagtgaaatc aaacttggca acagcttcca 120
taagcttgga tcctctagac ttatcgatc cgtcgtacag atcccgaccc atttgctgtc 180
caccagtcac gctagccata ccatgatgat gatgatgatg agaaccccc atggttaagct 240

<210> 10

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<221> SITE

<222> (1)

<223> lysyl residue bearing a biotin moiety

<220>

<223> Description of Artificial Sequence: Synthesised
peptide

<400> 10

Lys Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg

1

5

10

11

<210> 11

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<221> SITE

<222> (1)

<223> lysyl residue bearing a biotin moiety

<220>

<221> MOD_RES

<222> (7)

<223> PHOSPHORYLATION

<220>

<223> Description of Artificial Sequence: Synthesised
peptide

<400> 11

Lys Leu Leu His Ser Asp Tyr Met Asn Met Thr

1

5

10

<210> 12

<211> 81

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (1) .. (81)

<220>

<223> Description of Artificial Sequence: Polylinker

12

<400> 12

gct agg tcg acg gcc atg gta tcg atg aat tcc tgc agc ccg gcg cgc 48

Ala Arg Ser Thr Ala Met Val Ser Met Asn Ser Cys Ser Pro Ala Arg

1

5

10

15

tct gga tct act agt gcg gcc gcc acc gcg gtg

81

Ser Gly Ser Thr Ser Ala Ala Ala Thr Ala Val

20

25

<210> 13

<211> 27

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: Polylinker

<400> 13

Ala Arg Ser Thr Ala Met Val Ser Met Asn Ser Cys Ser Pro Ala Arg

1

5

10

15

Ser Gly Ser Thr Ser Ala Ala Ala Thr Ala Val

20

25

<210> 14

<211> 57

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (1)..(57)

<220>

<223> Description of Artificial Sequence: Polylinker

13

<400> 14

cat atg gcc atg gag gcc ccg gcg cgc tct gga tcc gtc gac ctg cag 48

His Met Ala Met Glu Ala Pro Ala Arg Ser Gly Ser Val Asp Leu Gln

1

5

10

15

cca agc taa

57

Pro Ser

<210> 15

<211> 18

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: Polylinker

<400> 15

His Met Ala Met Glu Ala Pro Ala Arg Ser Gly Ser Val Asp Leu Gln

1

5

10

15

Pro Ser

<210> 16

<211> 63

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (1)..(63)

<220>

<223> Description of Artificial Sequence: Polylinker

<400> 16

cat atg gcc atg gag gcc ccg ggg atc gga tcc gat ccg aat tcg agc 48

His Met Ala Met Glu Ala Pro Gly Ile Gly Ser Asp Pro Asn Ser Ser

1

5

10

15

14

tcg aga gat cta tga

63

Ser Arg Asp Leu

20

<210> 17

<211> 20

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: Polylinker

<400> 17

His Met Ala Met Glu Ala Pro Gly Ile Gly Ser Asp Pro Asn Ser Ser

1

5

10

15

Ser Arg Asp Leu

20

<210> 18

<211> 42

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 18

aggggaattcc tcgagtcatt ggggagtttc tgcattttct ag

42

<210> 19

<211> 38

<212> DNA

<213> Artificial Sequence

15

<220>

<223> Description of Artificial Sequence: Primer

<400> 19

catcgcgcgc agtaagagga gcaggctcct gcacagtg

38

<210> 20

<211> 58

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 20

tctcgttgga cccggtctac gtggagtcac gttcatgtag tcactgtgca ggagcctg 58

<210> 21

<211> 56

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 21

ccgggtccaa cgagaaagca ttaccagccc tatgcaccac ctagagactt cgcagc 56

<210> 22

<211> 49

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

16

<400> 22

catcgcgcg c tgcggccgct caggagcgat aggctgcgaa gtctctagg

49

<210> 23

<211> 58

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 23

tctcgttgga cccgggtctac gtggagtcac gttcatgaag tcactgtgca ggagcctg 58

<210> 24

<211> 58

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 24

tctcgttgga cccggtctac gtgcagtcac gttcatgtag tcactgtgca ggagcctg 58

<210> 25

<211> 56

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 25

gcgggtccaa cgagaaagca ttaccaggcc tatgcagcac ctagagactt cgcagc 56

17

<210> 26

<211> 29

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 26

catcgatcc gaagatttgc cccatcatg

29

<210> 27

<211> 28

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 27

catcgaattc tcatcgcttc tgctgtgc

28

<210> 28

<211> 34

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 28

catcgcgcg agtaagagga gcaggctcct gcac

34

18

<210> 29

<211> 62

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 29

tctcgttgga cccggtctac gtggagtcac gttcacgtag tcaactgtgca ggagcctgct 60
cc 62

<210> 30

<211> 62

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Primer

<400> 30

tctcgttgga cccggtctac gtggagtcac ttccacgtag tcaactgtgca ggagcctgct 60
cc 62

<210> 31

<211> 62

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 31

tctcgttgga cccggtctac gtggagtcac ttccacgtag tcaactgtgca ggagcctgct 60
cc 62

19

<210> 32

<211> 49

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 32

catcgcgcgcg gatccaagc ttatggaagc tgttgccaag tttgatttc 49

<210> 33

<211> 48

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 33

catcgaattc gtcgacgcgg ccgcttatcg ggcatgggt gccacgta 48

<210> 34

<211> 34

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 34

catcggatcc atagacatcc agtttcccaa atgg 34

20

<210> 35

<211> 34

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 35

catcgaattc ttactggtct tctcggttc tgtc

34

<210> 36

<211> 34

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 36

catcggatcc ttccttagag acagaaccgc agaa

34

<210> 37

<211> 37

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 37

catcgaattc ttaccaccgc actcgccctg ccgcctg

37

21

<210> 38

<211> 48

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 38

catcgcgggcc gcgtcgacga attcttatcg ggcatgggt gccacgta

48

<210> 39

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 39

accacagtcc atgccatcac

20

<210> 40

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 40

tccaccaccc tggtgctgta

20

22

<210> 41

<211> 31

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 41

gatctgtacg acgatgacga taagtctaga g

31

<210> 42

<211> 31

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 42

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31

<210> 43

<211> 47

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 43

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47

23

<210> 44

<211> 28

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 44

gatggaattc ttatcgggtc atgggtgc

28

<210> 45

<211> 77

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 45

gatggaattc agcacacagg acctcaccat gtacccatac gatgttccag attacgctga 60
agctgttgcc aagtttg

77

<210> 46

<211> 41

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 46

ataagatggc ggcgggatcc ttacataaac taagtgaaga g

41

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02738

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/47 A61K38/17 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL NUCLEOTIDE DATABASE, [Online] EBI, Hinxton, GB Trembl, ID 04376, 1 June 1998 (1998-06-01) BURGESS, J. ET AL.: "Growth factor receptor bound-protein 2like" retrieved from TREMBL Database accession no. 043726 XP002119673 abstract	1-5,13
P,X	WO 98 40482 A (INCYTE PHARMA INC ;BANDMAN OLGA (US); DIEGIDIO ANTHONY P (US)) 17 September 1998 (1998-09-17) claims 1-18 --- -/-	1-13

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *S* document member of the same patent family

Date of the actual completion of the international search

21 October 1999

Date of mailing of the international search report

11. 11. 99

Name and mailing address of the ISA

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Authorized officer

Nauche, S

INTERNATIONAL SEARCH REP RT

International Application No

PCT/GB 99/02738

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	QIU M, HUA S, AGRAWAL M, LI G, CAI J, CHAN E, ZHOU H, LUO Y, LIU M: "Molecular cloning and expression of human grap-2, a novel leukocyte-specific SH2- and SH3-containing" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 253, no. 2, 18 December 1998 (1998-12-18), pages 443-447, XP002119672 ORLANDO, FL US the whole document -----	1-5,13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 02738

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 10-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Information on patent family members

PCT/GB 99/02738

Form PCT/ISA/210 (patent family annex) (July 2002)